

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup>:</b> <b>A61K 47/10, 47/44, 37/02</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/25068</b> <b>(43) International Publication Date:</b> 10 November 1994 (10.11.94)
<b>(21) International Application Number:</b> PCT/CA94/00222 <b>(22) International Filing Date:</b> 22 April 1994 (22.04.94) <b>(30) Priority Data:</b> 247516 28 April 1993 (28.04.93) NZ <b>(71)(72) Applicant and Inventor:</b> SHERMAN, Bernard, Charles [CA/CA]; 50 Oldcolony Road, Willowdale, Ontario M2L 2K1 (CA). <b>(74) Agent:</b> JOHNSTON, N., Malcolm, S.; Malcolm Johnston & Associates, Suite 505, 133 Richmond Street West, Toronto, Ontario M5H 2L3 (CA).		<b>(81) Designated States:</b> AU, BB, BG, BR, BY, CA, CN, CZ, FL, GE, HU, JP, KG, KP, KR, KZ, LK, LV, MD, MG, MN, MW, NO, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>With amended claims.</i>
<b>(54) Title:</b> IMPROVED PHARMACEUTICAL ACCEPTABLE COMPOSITIONS CONTAINING AN ALCOHOL AND A HYDROPHOBIC DRUG  <b>(57) Abstract</b>  Pharmaceutical compositions having improved physical and absorption properties, wherein a hydrophobic drug is dissolved in a solvent system comprising at least one alcohol having a boiling point above 100 °C and a solubility in water inferior to 10 g per 100 g at 20 °C and a surfactant.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Improved pharmaceutical acceptable compositions containing an alcohol and an hydrophobic drug

### **TECHNICAL FIELD**

This invention is directed to pharmaceutical compositions which facilitate the in vivo absorption of hydrophobic drugs, including but not  
5 limited to polypeptide and protein drugs.

### **BACKGROUND ART**

The hydrophobic nature of some drugs causes them to be insoluble or  
10 poorly soluble in aqueous media. This reduces the absorption of the drug into systemic circulation after a composition containing the drug is swallowed, or the absorption into the target tissues upon topical application.

Previous attempts to deal with this problem have included forming a  
15 solution, either liquid or solid, incorporating the drug, whereby the drug is disseminated as molecular size particles within the solvent. If the solvent is water-soluble, upon ingestion of the composition the solvent dissolves and releases the drug as individual molecules which are more readily available for absorption than larger particles would be.

20

Problems previously encountered with this approach include:

- 1) Low solubility of the drug in a pharmaceutically acceptable solvent may require large quantities of solvent. This limits the amount  
25 of the drug that can be contained in a tablet or capsule of acceptable, swallowable size;

- 2 -

2) The composition may not be sufficiently stable on storage, and as a consequence the drug is precipitated and the efficacy diminishes; and

5 3) Upon ingestion of the composition, as the solvent in the composition dissolves in the gastrointestinal fluids, the drug may precipitate and agglomerate into larger particles that are poorly absorbed.

10 Among the drugs that are hydrophobic and give rise to such problems are nonpolar polypeptides, including cyclosporins, as defined in the Merck Index, Eleventh Edition. One such cyclosporin is cyclosporin A, also known as cyclosporine, and hereinafter referred to as "cyclosporine", known to be therapeutically active as an immunosuppressant.

15 U.S. Patent No. 4,388,307 discloses a composition comprising cyclosporine in an emulsion preconcentrate that is not water-soluble, but upon being mixed into gastrointestinal fluids forms an emulsion. The advantage of such compositions is that the cyclosporine in the emulsion is absorbed to a  
20 substantially greater extent than from other compositions previously known.

However, such compositions still suffer from certain disadvantages;

25 Although the absorption is superior to that of some compositions, the absorption is still less than the maximum possible and is variable.

Further, the concentration of cyclosporine in such compositions is limited to about 10 percent by weight. Hence, a capsule containing 100 mg

- 3 -

of cyclosporine weighs about 1 gram. Capsule strengths are thus limited to about 100 mg, as higher strength capsules would be too large to be swallowed.

Others have attempted to solve the formulation problems by developing solutions of cyclosporine (either liquid or solid solutions) that are entirely water-soluble and form a clear solution upon being dispersed in aqueous media such as gastrointestinal fluids.

European Patent Application No. 88305138.5 discloses use of a surfactant or solubilizing agent which is alphacyclodextrin or a derivative thereof.

Other publications and patent applications disclose compositions comprising cyclosporine together with surfactants, which also form clear solutions upon their addition to aqueous media.

However, such compositions have been generally impractical, as the quantities of surfactant needed to render cyclosporine entirely water-soluble have been unacceptably large. Typical therapeutic doses of such compositions would require toxic quantities of the surfactants.

Others have provided compositions in which surfactants are used in quantities less than sufficient to entirely solubilize the cyclosporine in water. Japanese Patent No. 1038029 discloses preparation of powders by dissolving cyclosporine and surfactants in organic solvents and evaporating the solvents. However, the compositions described do not fully solubilize the cyclosporine, and organic solvents are costly and more difficult to use than water in the manufacturing process.

- 4 -

U.K. Patent Application No. 8920597.5 discloses "microemulsion preconcentrates" which are stated to be improved over compositions disclosed in U.S. Patent No. 4,388,307. It is disclosed that a composition which, in addition to the active drug, comprises a hydrophilic phase, a lipophilic phase and a surfactant will, when added to water, disperse into an emulsion of smaller droplets than prior compositions, leading to superior absorption.

However, these formulations also have several limitations including:

- 1) The need to use several inactive ingredients;
- 2) The concentration of active drug that can be achieved is limited to about 15% in practice;
- 3) The ingredients that must be used and the quantities required may give rise to concerns about toxicity of the inactive ingredients; and
- 4) The absorption that can be achieved with practical formulations may still be less than optimum.

20

The emulsion preconcentrates disclosed in both U.S. Patent No. 4,388,307 and U.K. Patent Application No. 8920597.5 have the feature that they have a hydrophilic phase which is the primary solvent for the active drug. In U.S. Patent No. 4,388,307 the hydrophilic solvent is ethanol, and in British Application No. 8920597.5 other hydrophilic solvents are used such as Glycofurol 75, Transcutol, and Propylene Glycol.

- 5 -

The use of such hydrophilic solvents in emulsion preconcentrates is a cause of some of the limitations of such compositions disclosed in the prior art.

5           For example, when the emulsion preconcentrates are dispersed in water, some of the hydrophilic solvent can be drawn out of the emulsified phase and into solution in the water. Some of the active drug will be drawn along with the hydrophilic solvent and will precipitate as the solvent dissolves in the water. This precipitation reduces the quantity of the drug available for  
10       absorption.

          Furthermore, the use of a hydrophilic phase also requires the use of a hydrophobic or lipophilic phase in the emulsion preconcentrate to enable the formation of an emulsion, thus increasing the total quantity of inactive  
15       ingredients required, and this in turn also requires an increased quantity of surfactant in the emulsion preconcentrates.

          Furthermore, ethanol and other hydrophilic solvents previously used are relatively volatile and may evaporate from the composition on storage,  
20       resulting in precipitation of the drug. The compositions may thus have inadequate stability on storage unless specially packaged to prevent the evaporation.

          The term "drug" as used herein and in the accompanying claims is to  
25       be understood as meaning any pharmacologically active compound useful for the treatment or prevention of disease in humans or animals, including but not limited to nonpolar peptides.

- 6 -

The term "composition" as used herein and in the accompanying claims is to be understood as meaning any composition containing a drug along with inactive ingredients that are pharmaceutically acceptable by reason of not being excessively toxic in the quantity required; e.g. where oral administration is intended, acceptable for oral use, and where topical administration is intended, for topical use.

### **DISCLOSURE OF THE INVENTION**

10           The present invention is directed to pharmaceutical compositions which enable improved absorption of a hydrophobic drug while at the same time enabling the drug to be contained in the composition at relatively high concentrations.

15           In particular the present invention is directed to such compositions in the form of emulsions or emulsion preconcentrates, an emulsion preconcentrate being defined as a composition that, when added to water, readily disperses to form an emulsion.

20           An object of the invention is to eliminate the need to use a hydrophilic solvent as the primary solvent, in order to obviate the problems associated in the use of hydrophilic solvents as previously described.

25           For the purpose of this description, it will be understood that the term "solvent system" means the material in which the drug is dissolved. The solvent system may be a single solvent or a combination or mixture of ingredients included as solvents, surfactants, diluents, or for other purposes.

- 7 -

A primary feature of the invention is to use, as sole solvent or principal solvent in the solvent system, an alcohol that has a boiling point above 100°C, and that has a solubility in water of under 10 g per 100 g at 20°C. Such alcohols are less hydrophilic than ethanol or other solvents that have been previously used as the hydrophilic solvent in emulsion preconcentrates. Such alcohols will generally have 4 or more carbon atoms per molecule.

In view of the use of alcohols as solvent, it will be understood that the invention is applicable to drugs having adequate solubility in alcohols. Included among such drugs is cyclosporine.

Alcohols that may be used within the scope of the present invention may include any pharmaceutically acceptable alcohol having a boiling point above 100°C and a solubility in water of under 10 g per 100 g at 20°C. Preferably, the alcohol will have a boiling point above 150°C, and a solubility in water of under 5 g per 100 g at 20°C. Preferably the alcohol will have 6 to 16 carbon atoms per molecule. The use of alcohols having greater than 16 carbon atoms is generally impractical as they generally have melting points above 40°C. Suitable alcohols include but are not limited to 1-hexyl, 1-octyl, 2-octyl, 1-decyl, 1-dodecyl, 1-tetradecyl, benzyl and phenethyl alcohols.

Generally, as the number of carbon atoms per molecule is increased, alcohols become less hydrophilic and more hydrophobic. For example, ethyl alcohol (having 2 carbon atoms) is infinitely soluble in water at 20°C, whereas 1-butyl alcohol, (having 4 carbon atoms) has a solubility of only 7.9 g per 100 g of water, 1-hexyl (having 6 carbon atoms) has a solubility of only 0.6 g per 100 g, 1-octyl alcohol (having 8 carbon atoms) has a solubility of only 0.05 g per 100 g, and 1-decyl alcohol (having 10 carbon atoms) is essentially insoluble.

- 8 -

In addition to being less hydrophilic and more hydrophobic, the alcohols having more carbon atoms per molecule generally have higher boiling points and are less volatile at ambient temperature, so that use of alcohols with more carbon atoms per molecule can eliminate the problem of volatility of the hydrophilic solvents encountered with prior-art compositions.

In some applications of the invention it may be useful to use a combination of two or more alcohols instead of one. One alcohol may be selected as being superior as a solvent for the drug and another may be selected as superior for ease of dispersion in water. A combination of the two may be better than either alone to enable higher concentration of the drug and adequate ease of dispersion.

Another feature of the present invention is that the solvent system in which the drug is dissolved, in addition to including at least one alcohol meeting the aforesaid requirements, will include at least one pharmaceutically acceptable surfactant, which serves to make the composition dispersible in water to form an emulsion.

Examples of suitable surfactant are:

(i) Reaction products of natural or hydrogenated vegetable oils and ethylene glycol; i.e., polyoxyethylene glycolated natural or hydrogenated vegetable oils; for example polyoxyethylene glycolated natural or hydrogenated castor oils. Particularly suitable are the products designated in the United States Pharmacopoeia and National Formulary as Polyoxyl 35 Castor Oil and Polyoxyl 40 Hydrogenated Castor Oil, which are available under the trade names Cremaphor EL and Cremaphor RH40 respectively. Also suitable for use in this

- 9 -

category are the various tensides available under the trade name Nikkol, e.g. Nikkol HCO-60. The said product Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide.

- 5           (ii) Polyoxyethylene-sorbitan-fatty acid esters; e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g. products of the type known as polysorbates and commercially available under the trade name Tween.
- 10          (iii) Polyoxyethylene fatty acid esters; for example, polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj as well as polyoxyethylene fatty acid esters known and commercially available under the trade name Cetiol HE.
- 15          (iv) Polyoxyethylene-polyoxypropylene co-polymers, e.g. of the type known and commercially available under the trade names Pluronic and Emkalyx.
- 20          (v) Polyoxyethylene-polyoxypropylene block copolymers, e.g. of the type known and commercially available under the name Poloxamer.
- (vi) Dioctylsuccinate, dioctylsodiumsulfo succinate, di-[2-ethylhexyl]-succinate or sodium lauryl sulfate.
- 25          (vii) Phospholipids, in particular lecithins.
- (viii) Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol

- 10 -

laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth.

5 (ix) Bile salts; e.g. alkali metal salts, for example sodium taurocholate.

(x) Trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; e.g. of the type known and commercially available under the trade name Labrafil M1944CS.

10 (xi) Mono-, di- and mono/di-glycerides, especially esterification products of caprylic or capric acid with glycerol.

15 (xii) Sorbitan fatty acid esters; for example, of the type known and commercially available under the trade name Span.

20 (xiii) Pentaerythritol fatty acid esters and polyalkylene glycol ethers; for example pentaerythritedioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as pentaerythrite-fatty acid esters.

25 (xiv) Monoglycerides; e.g. glycerol monooleate, glycerol monopalmitate and glycerol monostearate; for example as known and commercially available under the trade names Myvatex, Myvaplex and Myverol, and acetylated, e.g. mono- and di-acetylated mono-glycerides; for example as known and commercially available under the trade name Myvacet.

(xv) Glycerol triacetate or (1,2,3)-triacetin; and

- 11 -

(xvi) Sterols and derivatives thereof, for example cholesterol and derivatives thereof, in particular phytosterols; e.g. products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof, such as known under the trade name Generol.

Suitable surfactants will not be limited to those listed above, but will be understood to include any compound which causes the composition to be more easily dispersible in water.

When the surfactant also is an effective solvent for the drug, it may be incorporated not only as surfactant, but as an additional carrier or co-solvent, to reduce the amount of alcohol required.

It will be understood that not all surfactants will act equally well with all alcohols to improve dispersion, and moreover, not all alcohols will work equally well as suitable solvents for all drugs. Determination of suitable combinations of alcohols and surfactants for particular applications within the scope of the invention will be within the capability of persons skilled in the art of product formulation.

Compositions in accordance with the invention may contain other ingredients in addition to the drug and one or more alcohols and one or more surfactants.

For example, the solvent system in which the drug is dissolved may include, in addition to one or more alcohols and one or more surfactants, one or more other ingredients that are interdissolved with the alcohol and surfactant and are included as co-solvents or diluents.

- 12 -

A composition in accordance with the invention may also contain, for example, a thickening agent (i.e., viscosity increasing agent). Suitable thickening agent (i.e., viscosity increasing agent). Suitable thickening agents may be of any of those known and employed in art, including, for example, pharmaceutically acceptable polymeric materials and inorganic thickening agents. However, where oral administration is intended, the use of thickening agents as aforesaid will generally not be required. Use of thickening agents is, on the other hand, indicated, e.g. where topical application is foreseen.

Compositions in accordance with the invention may also include one or more further ingredients; such as diluents, anti-oxidants, flavouring agents and so forth.

Compositions in accordance with the invention may be liquids at ambient temperatures or they may be solids prepared, for example, by use of alcohols or surfactants with melting points above ambient temperatures. The ingredients may be blended at temperatures above the melting point and then cooled to form solids. The solids may be ground into powder granules for further processing; for example, filling capsules or manufacture of tablets.

The capsules or tablets may be further processed by applying coatings thereto.

Especially where oral administration is contemplated, compositions in accordance with the invention may comprise end dosage forms for administration as emulsion preconcentrates. For example the emulsion preconcentrate may be directly used as liquid for oral ingestion, parenteral use, or topical application or it may be encapsulated into gelatin capsules for oral ingestion.

- 13 -

However, the present invention also provides pharmaceutical compositions in which the emulsion preconcentrate is further processed into an emulsion. Thus where oral administration is practiced, emulsions obtained, e.g. by diluting an emulsion preconcentrate with sufficient water or other aqueous medium (for example, a sweetened or flavoured preparation for drinking), may be employed as formulations for drinking. Similarly, where topical application is foreseen, compositions comprising an emulsion preconcentrate, a thickening agent, and water will provide an aqueous emulsion in gel, paste, cream or like form.

10

It should be noted that the droplet size of the emulsion formed when an emulsion preconcentrate according to the invention is dispersed in water will depend upon the identity and quantity of the ingredients used.

15

Generally, for a given composition, droplet size will decrease as the amount of surfactant is increased. Generally, smaller emulsion droplet size will enable improved absorption, so that there is usually an advantage to using more surfactant to obtain decreased droplet size. However, increased quantity of surfactant may also imply increased toxicity from the surfactant, increased cost and increased size of the dosage form of any desired strength. Moreover, if enough surfactant has been used to achieve absorption close to the maximum achievable, little is to be gained by adding more surfactant.

20

Hence, it will be understood that the quantity of the surfactant must be selected as sufficient to achieve maximum or near-maximum absorption without use of more than needed so as to avoid excessive toxicity, cost and dosage form size.

25

- 14 -

Compositions in accordance with the present invention whether emulsion preconcentrates or emulsions may be employed for administration in any appropriate manner and form; e.g. orally, as liquids or granules or in unit dosage form, for example in hard or soft gelatin encapsulated form, parenterally or topically; e.g. for application to the skin; for example in the form of a cream, paste, lotion, gel, ointment, poultice, cataplasm, plaster, dermal patch, powder, topically applicable spray, or the like, or for ophthalmic application; for example in the form of an eye-drop, lotion or gel formulation. Readily flowable forms may also be employed; e.g. for intralesional injection for the treatment of psoriasis, or may be administered rectally. Compositions in accordance with the invention are, however, primarily intended for oral or topical application, including application to the skin or eyes.

The relative proportion of drug and other ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned; e.g. whether it is an emulsion preconcentrate or emulsion, the route of administration, and so forth. The relative proportions will also vary, depending on the identity and particular function of ingredients in the composition; for example, in the case of a surfactant component of an emulsion preconcentrate, on whether this is employed as a surfactant only or both a surfactant and a co-solvent. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the product composition, e.g. in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of persons skilled in the art. All indicated proportions and relative weight ranges described herein are accordingly to be understood as being examples and not as not limiting the invention in its broadest aspect.

- 15 -

Compositions for topical use suitably comprise one or more carriers or diluents and/or other ingredients (e.g. thickening agents, emulsifying agents, preserving agents, moisturising agents, colourants and so forth) providing a suitable carrier.

5

Selection of excipients for the preparation of such formulations will, of course, be determined by the type of formulation desired as well as the particular condition to be treated, the area to be treated, and the effect desired. Some conditions will more suitably be treated with hydrophobic, e.g. fat-based compositions, for example compositions in accordance with the invention comprising a petrolatum based ointment or cream as carrier medium. In contrast, compositions for use in the treatment of some conditions will more appropriately be treated with more hydrophilic compositions, e.g. compositions in accordance with the invention in the form of an oil-in-water emulsion or gel.

15

Especially preferred compositions are compositions in which an emulsion concentrate is dispersed in a suitable pharmaceutically acceptable diluent or carrier. Compositions as aforesaid may take the form of a water-free or substantially water-free emulsion, i.e., comprise less than 10%, preferably less than 5%, most preferably less than 1% water.

20

Suitable carrier components include, for example:

25

- Solid hydrocarbons, for example petroleum jellies, e.g. white petrolatum, ceresin and solid paraffins, as well as waxes including animal, vegetable and synthetic waxes such as, for example, spermaceti, carnauba and bees wax;

- 16 -

- Liquid hydrocarbons, e.g. liquid paraffins and fatty acid esters such as isopropylmyristate and cetyl palmitate;
- Non-volatile silicones including silicone oils and pastes, and  
5 silicone-polyalkyleneoxide co-polymers for example such as known and commercially available under the trade name Piroethicon.

Such carrier components will suitably be present in the compositions in  
10 an amount of up to about 80%, e.g. from about 5 to about 70%, preferably from about 25 to about 60% by weight based on the total weight of the composition.

By use of suitable individual carrier ingredients or mixtures thereof,  
15 emulsions may be obtained in liquid or semi-solid form depending on, e.g., desired requirements for topical application.

Compositions for topical use may further comprise one or more consistency promoting agents, for example microcrystalline waxes, vegetable  
20 oils such as olive oils, corn oils and kernel oils, and vegetable oil derivatives including hydrogenated vegetable oils and vegetable oil partial-glycerides, e.g. in an amount of from about 0.1 to about 10%, preferably from about 1 to about 5% weight based on the total weight of the composition.

25 Such compositions will also suitably contain other ingredients which may include an anti-oxidant, and anti-bacterial agent, a stabilizer, and a skin penetration enhancer.

- 17 -

In addition to the foregoing the present invention also provides a process for the production of a pharmaceutical composition hereinbefore defined which process comprises bringing the individual components thereof into intimate admixture and, when required compounding the obtained composition in unit dosage form, for example filling said composition into soft or hard gelatin capsules, or dispersing the composition in a carrier which may include water.

### **BEST MODE OF CARRYING OUT THE INVENTION**

Preferred alcohols for use as principal solvent for the drug are alcohols having a boiling point above 150°C, a melting point under 40°, and a solubility in water of under 5 g per 100 g at 20°C. Especially preferred alcohols are 1-octyl, 2-octyl, 1-decyl, 1-dodecyl, 1-tetradecyl, benzyl and phenethyl alcohols.

Where two or more alcohols are to be used, a preferred combination is one selected from 1-octyl, 2-octyl, 1-decyl, 1-dodecyl, and 1-tetradecyl alcohols and another selected from benzyl and phenethyl.

Preferred surfactants are reaction products of natural or hydrogenated vegetable oils and ethylene glycol; i.e., polyoxyethylene glycolated natural or hydrogenated vegetable oils.

Especially preferred surfactants are polyoxyethylene glycolated natural or hydrogenated castor oils, including those designated in the United States Pharmacopoeia and National Formulary as Polyoxyl and Polyoxyl 40 Hydrogenated Castor Oil.

- 18 -

The invention will be more fully understood by the following examples which are illustrative but not limiting of compositions in accordance with the present invention.

5     EXAMPLE 1:

The following were placed in a test tube:

          cyclosporine 1.04 g;  
10        1-octyl alcohol 2.5 g; and  
          polyoxyl 40 hydrogenated castor oil 2.0 g.

Upon agitation, a clear solution was gradually formed.

15    EXAMPLE 2:

The following were placed in a test tube:

          cyclosporine 1.04 g;  
20        1-octyl alcohol 2.5 g; and  
          polyoxyl 35 castor oil 1.0 g.

Upon agitation, a clear solution was gradually formed.

25    EXAMPLE 3:

The following were placed in a test tube, after the 1-dodecyl was warmed to above 25°C:

- 19 -

cyclosporine 1.04 g;  
1-dodecyl alcohol 2.5 g; and  
polyoxyl 35 castor oil 1.0 g.

5           Upon agitation, a clear solution was gradually formed.

EXAMPLE 4:

The following were placed in a test tube:

10

cyclosporine 1.04 g;  
1-octyl alcohol 1.0 g;  
benzyl alcohol 0.25 g; and  
polyoxyl 35 castor oil 1.0 g.

15

Upon agitation, a clear solution was gradually formed.

EXAMPLE 5:

20           The following were placed in a test tube:

cyclosporine 1.04 g;  
1-decyl alcohol 1.0 g;  
benzyl alcohol 0.25 g; and  
25           polyoxyl 35 castor oil 1.0 g.

Upon agitation a clear solution was gradually formed.

EXAMPLE 6:

5       The following were placed in a test tube, after the 1-dodecyl alcohol  
was warmed to about 25°C:

          cyclosporine 5.20 g;  
          1-dodecyl alcohol 5.00 g;  
          benzyl alcohol 1.20 g; and  
10       polyoxyl 35 castor oil 5.00 g.

          Upon agitation a clear solution was gradually formed.

EXAMPLE 7:

15

          The following were placed in a test tube, after the 1-dodecyl alcohol  
was warmed to about 25°C:

          cyclosporine 1.04 g;  
20       1-dodecyl alcohol 1.0 g;  
          phenethyl alcohol 0.25 g; and  
          polyoxyl 35 castor oil 1.0 g.

          Upon agitation a clear solution was gradually formed.

25

          In the case of each of examples 1 to 7, the solution formed was readily  
dispersible in water to form an emulsion without precipitation of the  
cyclosporine.

- 21 -

The solution of example 6 was filled into hard gelatin capsules. The absorption was compared in human volunteers to that of Sandimmune (registered trademark) capsules which is the leading brand in the world market and made in accordance with U.S. Patent No. 4,388,307. This was done by  
5 performing a comparative bioavailability study in which capsules were ingested by human volunteers, blood samples were drawn and cyclosporine levels were measured. It was found that the extent of absorption of the composition of example 6 was substantially greater than that of Sandimmune (registered trademark).

10

The solutions of each of examples 1 to 7 are directly useable as drops for oral ingestion or as a liquid for ophthalmic or topical use.

Alternatively, they may be further processed in various ways previously  
15 described, including, for example, their incorporation into gelatin capsules or tablets for oral ingestion, or into emulsions and various other forms for oral or topical use.

For example, they may be incorporated into a cream, ointment, gel or  
20 the like by combination with further additives, e.g., thickening agents, paraffins, etc. as hereinbefore described.

The aforesaid examples use cyclosporine as the drug. However, similar compositions can be prepared using other drugs that are soluble in alcohols or  
25 in solvent systems containing alcohols and surfactants.

- 22 -

**INDUSTRIAL APPLICABILITY**

From the foregoing description it will be apparent that in the present  
5 invention there is provided an improved pharmaceutical composition which  
permits the more efficient administration and absorption of hydrophobic drugs.

- 23 -

**WHAT I/WE CLAIM IS:**

1. A water dispersible pharmaceutical composition comprising a drug dissolved in a solvent system, said solvent system comprising at least one alcohol having a boiling point above 100°C and a solubility in water of less than 10 g per 100 g at 20°C and at least one surfactant.
2. A composition according to Claim 1 wherein the alcohol has a boiling point above 150°C and a solubility in water inferior to 5 g per 100 g at 20°C.
3. A composition according to Claim 1 or 2 wherein the drug is hydrophobic.
4. A composition according to any of Claims 1 to 3 wherein the drug is a nonpolar peptide.
5. A pharmaceutical composition according to Claim 4 wherein the peptide is a monocyclic peptide.
6. A composition according to any of Claims 1 to 5 wherein the drug is a cyclosporin.
7. A composition according to Claim 6 wherein the drug is cyclosporine.
8. A composition according to any of Claims 1 to 7 wherein said alcohol has 6 to 16 carbon atoms per molecule.
9. A composition according to Claim 8 wherein said alcohol has 7 to 14 carbon atoms per molecule.

- 24 -

10. A composition according to Claim 9 wherein the alcohol is selected from 1-octyl, 2-octyl, 1-decyl, 1-dodecyl, 1-tetradecyl, benzyl and phenethyl.
11. A composition according to Claim 10 wherein the alcohol is selected  
5 from 1-decyl, 1-dodecyl and 1-tetradecyl.
12. A composition according to any of Claims 1 to 10 containing two or more such alcohols.
- 10 13. A composition according to Claim 12 wherein one alcohol is selected from 1-octyl, 2-octyl, 1-decyl, 1-dodecyl, 1-tetradecyl, and another is selected from benzyl and phenethyl.
14. A composition according to Claim 13 wherein one alcohol is selected  
15 from 1-decyl, 1-dodecyl and 1-tetradecyl and the other is benzyl.
15. A composition according to Claim 13 wherein one alcohol is selected from 1-decyl, 1-dodecyl and 1-tetradecyl and the other is phenethyl.
- 20 16. A composition according to any of Claims 1 to 15 wherein the quantity of such alcohol or alcohols is at least 10% by weight of the solvent system.
17. A composition according to Claim 16 wherein the quantity of such alcohol or alcohols is at least 20% by weight of the solvent system.
- 25 18. A composition according to Claim 17 wherein the quantity of such alcohol or alcohols is at least 40% by weight of the solvent system.

- 25 -

19. A composition according to Claim 18 wherein the quantity of such alcohol or alcohols is at least 60% by weight of the solvent system.
20. A composition according to any of Claims 1 to 19 wherein the  
5 surfactant is a polyoxyethylene glycolated natural or hydrogenated vegetable oil.
21. A composition according to Claim 20 wherein the surfactant is a polyoxyethylene glycolated natural or hydrogenated castor oil.
- 10 22. A pharmaceutical composition according to any of Claims 1 to 21 which is dispersed in a carrier.
23. A pharmaceutical composition according to Claim 22 wherein the  
15 carrier is water or contains water.
24. A pharmaceutical composition according to any of Claims 1 to 22 which when dispersed in a carrier forms an emulsion.
- 20 25. A pharmaceutical composition according to any of Claims 1 to 24 adapted for oral administration.
26. A composition according to any of Claims 1 to 25 in a liquid form.
- 25 27. A composition according to any of Claims 1 to 26 contained within a gelatin capsule.
28. A pharmaceutical composition according to any of Claims 1 to 25 which is made into the form of a tablet.

- 26 -

29. A composition according to Claims 1 to 24 adapted for topical or  
ophthalmic administration.

30. A composition according to Claim 29 in a powder, liquid, cream,  
5 ointment or spray form.

31. A composition according to any of Claims 1 to 20 adapted for  
parenteral administration.

## AMENDED CLAIMS

[received by the International Bureau on 29 September 1994 (29.09.94);  
original claims 1-31 replaced by amended claims 1-24 (3 pages)]

- 5 1. A water-dispersible pharmaceutical composition comprising a drug  
dissolved in a solvent system, said solvent system comprising at least one  
alcohol selected from saturated alkyl alcohols having at least 6 carbon atoms  
per molecule and said solvent system further comprising at least one  
surfactant, said drug having solubility in water of less than 1 part per 1000  
10 parts by weight at 25° and solubility in at least one such alcohol of at least  
1 part per 100 parts by weight at 25°C, said solvent system optionally  
comprising other ingredients.
2. A composition as in Claim 1 wherein the amount by weight of said  
15 drug and the total amount by weight of said alcohols each exceeds two percent  
of the total weight of the composition.
3. A composition as in Claim 1 wherein the amount by weight of said  
drug and the total amount by weight of said alcohols each exceeds four percent  
20 of the total weight of the composition.
4. A composition as in Claim 1 wherein the amount by weight of said  
drug and the total amount by weight of said alcohols each exceeds eight  
percent of the total weight of the composition.  
25
5. A composition according to any of Claims 1 to 4 wherein said alcohol  
has from 6 to 14 carbon atoms per molecule.
6. A composition according to any of Claims 1 to 5 wherein the total  
30 amount by weight of said alcohols is greater than the total amount by weight

of alcohols that have one hydroxyl group per molecule and that are not saturated alkyl alcohols having at least 6 carbon atoms per molecule.

5 7. A composition according to any of Claims 1 to 6 wherein said solvent system comprises an alcohol selected from 1-octyl, 2-octyl, 1-decyl, and 1-dodecyl alcohols.

8. A composition according to any of Claims 1 to 7 wherein said drug is a peptide.

10

9. A composition according to any of Claims 1 to 7 wherein said drug is a monocyclic peptide.

10. A composition according to any of Claims 1 to 7 wherein said drug is a cyclosporin.

15

11. A composition according to any of Claims 1 to 7 wherein said drug is cyclosporine.

20 12. A composition according to any of Claims 1 to 11, wherein said solvent system comprises 1-decyl alcohol.

13. A composition according to any of Claims 1 to 11, wherein said solvent system comprises 1-dodecyl alcohol.

25

14. A composition according to any of Claims 1 to 13 wherein said solvent system comprises at least two alcohols.

## 29

15. A composition according to any of Claims 1 to 13 wherein said solvent system further comprises an alcohol selected from benzyl and phenethyl alcohols.
- 5 16. A composition according to any of Claims 1 to 15 wherein said surfactant is a polyoxyethylene glycolated natural or hydrogenated vegetable oil.
- 10 17. A composition according to any of Claims 1 to 15 wherein said surfactant is a polyoxyethylene glycolated natural or hydrogenated castor oil.
18. A composition according to any of Claims 1 to 17 which is dispersed in a carrier.
- 15 19. A composition according to Claim 18 wherein the carrier is water or contains water.
20. A composition according to any of Claims 1 to 19 in a liquid form.
- 20 21. A composition according to any of Claims 1 to 20 contained within a gelatin capsule.
22. A composition according to any of Claims 1 to 21 adapted for oral administration.
- 25 23. A composition according to any of Claims 1 to 20 adapted for topical or ophthalmic administration.
24. A composition according to any of Claims 1 to 20 adapted for  
30 parenteral administration.

## INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/CA 94/00222

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 5 A61K47/10 A61K47/44 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 09299 (BIOGAL GYOGYSZERGYAR RT.) 11 June 1992 see page 10; example 3 ---	1-7, 16-19
X	PATENT ABSTRACTS OF JAPAN vol. 17, no. 367 (C-1082)12 July 1993 & JP,A,05 058 906 (HATA K. ET AL) 9 March 1993 see abstract ---	1-7, 20-26,29
X	DATABASE WPI Section Ch, Week 8711, Derwent Publications Ltd., London, GB; Class B04, AN 87-074911 & JP,A,62 026 220 (HISHIYAMA S. K.) 4 February 1987 see abstract ---	1-3, 8-10,16, 20-22,31
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 July 1994

Date of mailing of the international search report

02.08.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

Boulois, D

## INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/CA 94/00222

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 218 334 (SANDOZ LTD) 15 November 1989  see page 4, line 11 - line 24 see page 12; example 1.1 see page 14 - page 15; example 3 ----	1-8,12, 16,17, 22-24, 26,30
X	DATABASE WPI Section Ch, Week 7819, Derwent Publications Ltd., London, GB; Class A10, AN 78-33884A & JP,A,53 032 109 (TAKEDA CHEMICAL IND KK) 27 March 1978 see abstract ----	1-3, 8-10,12, 20,21,31
X	BE,A,684 058 (TAISHO PHARMACEUTICAL CO) 13 July 1966  see page 4; examples 2,3 ----	1-5, 8-10,12, 16, 20-24, 26,31
X	FR,A,2 636 534 (SANDOZ SA) 23 March 1990 cited in the application  & GB8920597 see page 60; example 1.3 ----	1,3-7, 16,17, 20-28
X	FR,A,2 678 169 (SANDOZ SA) 31 December 1992 see page 20 - page 22; example 2 -----	1-7,16, 17,20-28

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 94/00222

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9209299	11-06-92	AU-A-	8944091	25-06-92
		EP-A-	0512109	11-11-92
		JP-T-	5503306	03-06-93
-----				
GB-A-2218334	15-11-89	BE-A-	1002266	13-11-90
		CH-A-	679119	31-12-91
		DE-A-	3915617	16-11-89
		FR-A-	2631235	17-11-89
		JP-A-	2017127	22-01-90
-----				
BE-A-684058	13-01-67	DE-A-	1617871	08-04-71
		FR-M-	7188	18-08-69
		GB-A-	1112567	
		NL-A-	6610014	16-01-67
		US-A-	3499088	03-03-70
-----				
FR-A-2636534	23-03-90	AU-B-	627220	20-08-92
		AU-A-	4140089	22-03-90
		CH-A-	679118	31-12-91
		DE-A-	3930928	22-03-90
		GB-A, B	2222770	21-03-90
		IL-A-	91642	12-04-94
		JP-A-	2121929	09-05-90
		LU-A-	87586	07-05-91
		NL-A-	8902315	17-04-90
		SE-A-	8903042	11-05-90
-----				
FR-A-2678169	31-12-92	AU-A-	1852792	11-03-93
		CA-A-	2072509	28-12-92
		DE-A-	4219526	18-03-93
		EP-A-	0539319	28-04-93
		FR-A-	2685706	02-07-93
		GB-A-	2257359	13-01-93
		JP-A-	5186365	27-07-93